201-14711

Crompton

Product Safety and Regulatory Affairs

August 27, 2003

Marianne L. Horinko
Acting Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116

Attn: Chemical Right-To-Know Program

Dear Administrator Horinko,

Crompton Corporation is submitting the enclosed Robust Summary and Test plan for the following chemical:

Dimethyl 3,3'-thiobispropionate (CAS # 4131-74-2).

If you have any questions, please contact me at 203-573-3390 or e-mail to mark_thomson@cromptoncorp.com

Sincerely

Dr. Mark A. Thomson
Manager, Toxicology & International Product Registration
Crompton Corporation
Middlebury, CT 06749
USA

Responsible Care®
A Public Commitment

201-14711A

HIGH PRODUCTION VOLUME (HPV) CHEMICAL CHALLENGE PROGRAM

TEST PLAN

For

Dimethyl 3,3'-thiobispropionate

CAS No. 4131-74-2

Submitted to the US EPA

BY

Crompton Corporation.

1. General Information

1.1 CAS Number: 4131-74-2

1.2 Molecular Weight: 206.26

1.3 Structure and formula: $C_8H_{14}O_4S$

$S(CH_2CH_2CO_2CH_3)_2$

1.4 Introduction

Dimethyl 3,3'-thiobispropionate is used as an antioxidant in PVC systems.

2. Justification for Use of Read Across Data for Human Health Toxicity Endpoints

Studies have been reported in the literature concerning the metabolism of thiodipropionic acid (TDPA) and its esters (see robust summary section 5). These studies show that esters of TDPA are almost completely absorbed and hydrolysed to TDPA, which itself is largely eliminated in the urine, either as the free acid or as an acid labile conjugate. Absorption of the various esters of TDPA is not significantly affected by the water solubility as demonstrated by the high degree of absorption of one analog, didodecyl 3,3'-thiodipropionate (insoluble in water), following oral administration in the rat. Radiolabeled studies show esters of TDPA will undergo hydrolytic cleavage. This process can occur to a significant extent within the gastrointestinal tract. It is therefore likely that any toxicity, or lack of toxicity, will be as a consequence of exposure to hydrolytic degradants, particularly the parent acid. It can be predicted that TDPA will be the most significant degradant following oral ingestion of dimethyl 3,3'-thiodipropionate, therefore the toxicity of this product has been evaluated indirectly from toxicity studies with didodecyl 3,3'-thiodipropionate.

3. Review of Existing Data and Development of Test Plan

Crompton Corporation has undertaken a comprehensive evaluation of all relevant data on the SIDS endpoints of concern for dimethyl 3,3'-thiobispropionate and structural analogs.

The availability of the data on the specific SIDS endpoints is summarized in Table 1. Table 1 also shows data gaps that will be filled by additional testing.

Table 1: Available adequate data and proposed testing on Dimethyl 3,3'-thiobispropionate

CAS No. 10081-67-1	Information Available?	GLP	OECD Study?	Other Study?	Estimation Method?	Acceptable?	SIDS Testing required?
	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
Physicochemical							
Melting Point	Y	N			Y	Y	N
Boiling Point	Y	N			Y	Y	N
Vapour Pressure	Y	N			Y	Y	N
Water Solubility	Y	N			Y	Y	N
Partition Coefficient (Kow)	Y	N			Y	Y	N
Environmental Fate							
Biodegradation	Y				Y	Y	N
Hydrolysis	Y				Y	Y	N
Photodegradation	Y				Y	Y	N
Transport and Distribution between Environmental Compartments	Y				Y	Y	N
Ecotoxicology							
Acute Fish	Y				Y	Y	N
Acute Daphnia	Y				Y	Y	N
Acute Algae	Y				Y	Y	N
Toxicology							
Acute Oral	Y*					Y	N
Repeat Dose toxicity	Y*					Y	N
Genetic toxicity – Gene mutation	N						Y
Genetic toxicity – Chromosome aberration	N						Y
Reproductive toxicity	Y*					Y	N
Developmental toxicity/teratogenicity	Y*					Y	N

* Data available on analogs

A. Evaluation of Existing Physicochemical Data and Proposed Testing

1. Melting Point

The substance is a liquid at room temperature. The melting point is estimated to be –38.3°C using MPBPWIN v1.40.

2. Boiling Point

The boiling point is estimated to be 242°C using MPBPWIN v1.40.

3. Vapour Pressure

The vapour pressure is estimated to be 0.055 hPa at 25°C using MPBPWIN v1.40.

4. Water Solubility

The MSDS for dimethyl 3,3'-thiodipropionate states that it is practically insoluble in water.

5. Partition Coefficient

The partition coefficient is estimated as log Kow = 0.98 using KOWWIN v1.66.

Summary of Physicochemical Properties Testing: Existing data for melting point, boiling point, vapour pressure, water solubility and partition coefficient are considered to fill these endpoints adequately. No additional testing is recommended.

B. Evaluation of Existing Environmental Fate Data and Proposed Testing

1. Biodegradation

The biodegradability of the chemical has been estimated using Biowin v4.00 and the results indicate the chemical to be readily biodegradable.

2. Hydrolysis

The half life is estimated to be 1.02 years at pH7 using HYDROWIN v1.67.

3. Photodegradation

The potential for photodegradation has been estimated using the AOPWIN v1.90, and indicates atmospheric oxidation via OH radicals reaction with a half-life of 6.2 hours.

4. Transport and Distribution between Environmental Compartments

An Epiwin Level III Fugacity Model calculation has been conducted for the chemical and indicates distribution mainly to water and soil for emissions of 1000 kg/hr simultaneously to air water and soil compartments.

Summary of Environmental Fate Testing: The endpoints for biodegradation, hydrolysis, photodegradation and transport and distribution between environmental compartments are filled adequately. No additional testing is recommended.

C. Evaluation of Existing Ecotoxicity Data and Proposed Testing

1. Acute Toxicity to Fish

The LC50 (96 h) is estimated to be 109.7 mg/L, calculated using ECOSAR v0.99g.

2. Acute Toxicity to Algae

The EC50 (96 h) is estimated to be 8.41 mg/L, calculated using ECOSAR v0.99g.

3. Acute Toxicity to Daphnia

The EC50 (48 h) is estimated to be 1388.7 mg/L, calculated using ECOSAR v0.99g.

Summary of Ecotoxicity Testing: No further ecotoxicity testing is recommended due to the extremely low water solubility and high estimated log K_{ow} value. The ecotoxicity endpoints are considered to be adequate.

D. Evaluation of Existing Human Health Effects Data and Proposed Testing

1. Acute Oral Toxicity

The LD_{50} (rat) has been reported as between >2500 and >5000 mg/kg b.w. and LD50 (mouse) as >2000 in studies conducted using the analog didodecyl 3,3'-thiodipropionate. In studies using the parent thiodipropionic acid, LD_{50} (mouse) of 2000 mg/kg b.w. and LD50 (rat) of 3000 mg/kg b.w. were reported.

2. Repeat Dose Toxicity

In a repeat dose toxicity study (oral, 13 weeks, rat) using the analog didodecyl 3,3'-thiodipropionate a NOAEL of 350 mg/kg b.w./day was reported.

3. Genotoxicity

An Ames test will be conducted using OECD 471.

An in vitro chromosome aberration study will be conducted using OECD Method 473.

4. Reproductive and Developmental Toxicity

In a study using the analog didodecyl 3,3'-thiodipropionate (oral, 13 week, rat) no adverse effects were seen in the reproductive organs of the test animals up to and including the high dose of 1000 mg/kg b.w./day. This is suggestive of no adverse effects on reproduction.

Developmental toxicity studies have been conducted using the analog didodecyl 3,3'-thiodipropionate (oral, essentially following OECD 414, rat, mouse, rabbit, hamster). In all these studies, no adverse effects were seen in the parents or the offspring at the highest dose used.

Summary of Human Health Effects Testing: The potential to cause in vitro chromosomal aberrations will be determined using OECD Method 473 and an Ames test will be performed using OECD Method 471. Existing data for the analog substance and parent thiopropionic acid are considered to fill the remaining endpoints adequately.

3. Evaluation of Data for Quality and Acceptability

The collected data were reviewed for quality and acceptability following the general US EPA guidance [2] and the systematic approach described by Klimisch et al [3]. These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation [4]. The codification described by Klimisch specifies four categories of reliability for describing data adequacy. These are:

(1) Reliable without restriction: Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

(2) Reliable with Restrictions: Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

(3) Not Reliable: Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.

(4) Not Assignable: Includes studies or data in which insufficient detail is reported to assign a rating, e.g. listed in abstracts or secondary literature.

4. References

[1] US EPA, EPI Suite Software, 2000

[2] USEPA (1998). Guidance for Meeting the SIDS Requirements (The SIDS Guide). Guidance for the HPV Challenge Program. Dated 11/2/98.

[3] Klimisch, H.-J., et al (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. Regul. Toxicol. Pharmacol. 25:1-5

[4] USEPA (1999). Determining the Adequacy of Existing Data. Guidance for the HPV Challenge Program. Draft dated 2/10/99.

201-14711B

IUCLID

Data Set

Robust Summaries

Existing Chemical	:	ID: 4131-74-2
CAS No.	:	4131-74-2
EINECS Name	:	dimethyl 3,3'-thiobispropionate
EC No.	:	223-948-9
Molecular Formula	:	C8H14O4S
Status	:	
Memo	:	Mark 5152 US HPV Crompton Corporation
Printing date	:	25.06.2003
Revision date	:	
Date of last update	:	25.06.2003
Number of pages	:	18
Chapter (profile)	:	Chapter: 2, 3, 4, 9
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

2.1 MELTING POINT

Value	:	-38.3 °C
Sublimation	:	
Method	:	other: Estimation using MPBPWIN v1.40
Year	:	2003
GLP	:	
Test substance	:	Dimethyl 3,3'-thiobispropionate (CAS No. 4131-74-2)
Remark	:	Subtance is a liquid at room temperature.
Reliability	:	(2) valid with restrictions

27.03.2003 (9)

2.2 BOILING POINT

Value	:	242 °C at
Decomposition	:	
Method	:	other: Estimation using MPBPWIN v1.40
Year	:	2003
GLP	:	
Test substance	:	Dimethyl 3,3'-thiobispropionate (CAS No. 4131-74-2)
Reliability	:	(2) valid with restrictions

27.03.2003 (9)

2.4 VAPOUR PRESSURE

Value	:	.055 hPa at 25 °C
Decomposition	:	
Method	:	other (calculated): MPBPWIN v1.40
Year	:	2003
GLP	:	
Test substance	:	Dimethyl 3,3'-thiobispropionate (CAS No. 4131-74-2)
Reliability	:	(2) valid with restrictions

27.03.2003 (9)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	octanol-water
Log pow	:	.98 at °C
pH value	:	
Method	:	other (calculated): KOWWIN v1.66
Year	:	2003
GLP	:	
Test substance	:	Dimethyl 3,3'-thiobispropionate (CAS No. 4131-74-2)
Reliability	:	(2) valid with restrictions

27.03.2003 (9)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Description	:	not soluble
Method	:	other: unknown
Year	:	2002
GLP	:	no data

Test substance : Dimethyl 3,3'-thiobispropionate (CAS No. 4131-74-2)
Reliability : (4) not assignable
08.05.2003 (2)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
DIRECT PHOTOLYSIS		
Halflife t1/2	:	6.2 hour(s)
Degradation	:	% after
Quantum yield	:	
Deg. product	:	
Method	:	other (calculated): AOPWIN v1.90
Year	:	2003
GLP	:	
Test substance	:	Dimethyl 3,3'-thiobispropionate (CAS No. 4131-74-2)
Remark	:	Concentration of hydroxyl radicals in air = 1.5E6 OH/cm3 12-hour day

27.03.2003 (9)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	at °C
t1/2 pH7	:	at °C
t1/2 pH9	:	at °C
Deg. product	:	
Method	:	other (calculated): Estimated using HYDROWIN v1.67
Year	:	2003
GLP	:	
Test substance	:	Dimethyl 3,3'-thiobispropionate (CAS No. 4131-74-2)
Result	:	Half life at pH 8: 37.14 days Half life at pH 7: 1.02 years
Reliability	:	(2) valid with restrictions

27.03.2003 (9)

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	fugacity model level III
Media	:	
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Method	:	other: Calculation using EPIWIN Level III Fugacity Model
Year	:	2003
Test condition	:	Henry's Law Constant: 3.15E-10 atm-m3/mole (Henrywin program) Vapor pressure: 0.0417 mmHg (Mpbpwin program) Log Kow: 0.98 (experimental value) Soil Koc: 3.92 (calc by model) 1000 kg/hr emissions to air, water and soil compartments.
Test substance	:	Dimethyl 3,3'-thiobispropionate (CAS No. 4131-74-2)

	Mass Amount (percent)	Half-life (hr)	Emissions (kg/hr)
Air	0.01	12.4	1000
Water	42	360	1000
Soil	57.9	360	1000
Sediment	0.0757	1.44E+3	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	1.51E-13	7.17	1.28	0.239	0.0426
Water	4.09E-15	1.03E+3	536	34.4	17.9
Soil	1.59E-13	1.42E+3	0	47.4	0
Sediment	3.37E-15	0.465	0.0193	0.0155	0.000645

Persistence time: 425 hr
Reaction time: 518 hr
Advection time: 2.38E+3 hr
Percent reacted: 82.1
Percent advected: 17.9

Half-lives (hr), (based upon Biowin (ultimate) and Aopwin):
Air: 12.36
Water: 360
Soil: 360
Sediment: 1440
Biowin estimate: 3.024 (weeks)

Advection times (hr):
Air: 100
Water: 1000
Sediment: 5E+4

Reliability : (1) valid without restriction
27.03.2003 (9)

3.5 BIODEGRADATION

Type : aerobic
Inoculum :
Deg. product :
Method : other: estimation using BIOWIN v4.00
Year : 2003
GLP :
Test substance : Dimethyl 3,3'-thiobispropionate (CAS No. 4131-74-2)

Result : MITI Linear Biodegradation Probability = 0.9845
MITI Non-linear Biodegradation Probability = 0.9616

The substance is predicted to be readily biodegradable

Reliability : (2) valid with restrictions
27.03.2003 (9)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	
Species	:	
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	109.7
Method	:	other: Estimated using ECOSAR v0.99g
Year	:	2003
GLP	:	
Test substance	:	Dimethyl 3,3'-thiobispropionate (CAS No. 4131-74-2)
Test condition	:	Log Kow: 0.98 (KOWWIN estimate) Water solubility: 1E+4 mg/l Ecosar Class: Esters
Reliability	:	(2) valid with restrictions

27.03.2003 (9)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	
Species	:	Daphnia sp. (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	1388.7
Method	:	other: Estimated using ECOSAR v0.99g
Year	:	2003
GLP	:	
Test substance	:	Dimethyl 3,3'-thiobispropionate (CAS No. 4131-74-2)
Test condition	:	Log Kow: 0.98 (KOWWIN estimate) Water solubility: 1E+4 mg/l Ecosar Class: Esters
Reliability	:	(2) valid with restrictions

27.03.2003 (9)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	
Endpoint	:	
Exposure period	:	96 hour(s)
Unit	:	mg/l
EC50	:	8.41
Method	:	other: Estimated using ECOSAR v0.99g
Year	:	2003
GLP	:	
Test substance	:	Dimethyl 3,3'-thiobispropionate (CAS No. 4131-74-2)
Test condition	:	Log Kow: 0.98 (KOWWIN estimate) Water solubility: 1E+4 mg/l Ecosar Class: Esters
Reliability	:	(2) valid with restrictions

27.03.2003 (9)

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In Vitro/in vivo	:	In vivo
Type	:	
Species	:	rat
Number of animals		
Males	:	
Females	:	
Doses		
Males	:	
Females	:	
Vehicle	:	
Method	:	
Year	:	1973
GLP	:	no
Test substance	:	Thiodipropionic acid (CAS No. 111-17-1) Didodecyl thiodipropionate (CAS No. 123-28-4) POLY-TDPS-2000

[1-^{14}C]Thiopropionic acid ([^{14}C]TDPA] of specific activity 1.71 mCi/mmol was used to prepare ^{14}C-labeled POLY_TDPS-2000 ([^{14}C]TDPS) of specific activity 5µCi/mg (equivalent to 58% TDPA).

Carboxy ^{14}C-labeled didocyl thiodipropionate ([^{14}C]DDTDP), specific activity 60 µCi/mmol. was purified (99.2%) by recrystallization from aqueous acetone.

Method : Animals: Male Sprague-Dawley rats weighing 215-325 g were housed in glass metabolism chambers fitted for the collection of urine, feces and respiratory CO_2.

Dosages: In some experiments the dose was incorporated into feed. Starved rats were given the food and CO_2 collection was started. After 4-8 hr any unconsumed dose was removed and rats were returned to the regular diet.

In other experiments the dissolved dose was intubated in to the stomach. [^{14}C]TDPA was dissolved in ethanol-water (1:1) and [^{14}C]DDTDP in corn oil.

Urines and feces in the [^{14}C]TDPS study were collected at the end of dosing and then at 24 hr intervals. [^{14}C]TDPA and [^{14}C]DDTDP experiment urines and CO_2 absorbers were processed daily. Liver, kidneys, brain, heart, lungs, whole gastrointestinal tracts and fat samples were removed at sacrifice and frozen with carcasses until assayed.

Result : Elimination of radioactivity:

[^{14}C]TDPA and [^{14}C]TDPS were almost entirely absorbed from the gastrointestinal tract when fed at levels of 3-6 mg/kg, and [^{14}C]TDPA and [^{14}C]DDTDP were almost entirely absorbed at levels up to 650 and 210 mg/kg, respectively (Table 1). Urinary excretion represented the major pathway of disposal for all 3 materials, generally accounting for 90% of the total eliminate in all experiments. Elimination of radioactivity as $^{14}CO_2$ was significant in all experiments, amounting to about 5% of the dose. Elimination was very rapid. Over 90% of the total radioactivity eliminated was eliminated in less than 24 hour by all rats (Table 2). The excretion patterns and rates did not appear to be dose-related (Table 1).

Distribution of radioactivity in organs at sacrifice:

Levels of radioactivity of organs from rats fed [^{14}C]TDPS were slightly elevated at 4 days but had decreased to normal by 34 days. The value in fat was somewhat higher than the other tissue values at 4 days but had decreased to the same levels as the other tissues by 34 days. Rats fed [^{14}C]TDPA and [^{14}C]DDTDP had tissue radioactivity values throughout which were close to normal values except that the value of radioactivity in the fat of rats fed [^{14}C]DDTDP were elevated at 4 days after dosing and remained so at 8 and 34 days.

Nature of the radioactive urinary metabolites of [^{14}C]TDPA, [^{14}C]TDPS and [^{14}C]DDTDP:

Thin-layer and paper chromatography of urine for metabolite detection was unsuccessful because of the tendency of TDPA to migrate as more than one spot with most solvent systems. In consequence, reverse isotope dilution studies were carried out with untreated and hydrolyzed urines to assay elimination of free and combined [^{14}C]TDPA (Table 2). Acid hydrolyses were performed without added TDPA in the [^{14}C]TDPS studies, but after addiion of TDPA in the [^{14}C]TDPA and [^{14}C]DDTDP experiments. Assays of untreated urines from rats fed [^{14}C]TDPA and [^{14}C]TDPS at low dose levels (3.1 and 5.6 mg/kg) showed only a small portion of the radioactivity was eliminated as free TDPA. At high dose levels (627 mg/kg), most of the excreted radioactivity was free TDPA. Acid hydrolysis of urine samples afforded high recovery of radioactivity as TDPA, approaching 10% of the urinary radioactivity after feeding [^{14}C]TDPA and [^{14}C]DDTDP and 70% after [^{14}C]TDPS.

To determine whether the combined radioactivity was present as an ester glucuronide, a urine sample from a rat fed [^{14}C]TDPS at the low level was hydrolyzed with ß-glucuronidase. [^{14}C]TDPA amounted to 14.4% of the urinary radioactivity compared to 7.0% without treatment. Mild alkaline hydrolysis was unsuccessful and led to decomposition of TDPA.

The results show that oral doses of [^{14}C]TDPA in the range of 3-650 mg/kg are almost entirely and rapidly absorbed from the gastrointestinal tract of the rat, and that the absorbed [^{14}C]TDPA is very rapidly eliminated in the urine with only a small amount entering an oxidative metabolic pathway.

Reverse isotope dilution studies indicate that [^{14}C]TDPA is excreted in the urine either largely unchanged (627 mg/kg dose) or as an acid labile conjugate (3.1 mg/kg dose) which is apparently not a glucuronide.

The disposition of [^{14}C]TDPA combined as part of the TDPS or DDTDP molecules was very similar to the disposition of orally intubated free [^{14}C]TDPA. The rapidity of elimination, the relative importance of the various pathways, and the tissue retentions for each substance were not apparently different. At least 65% of ingested [^{14}C]TDPS appeared as free or combined [^{14}C]TDPA in the urine, the metabolites apparently being identical with those found after feeding [^{14}C]TDPA. Similarly, [^{14}C]DDTDP was also excreted as free [^{14}C]TDPA or an acid labile conjugate. The identification of only 65% of the urinary radioactivity in the [^{14}C]TDPS study as free or combined [^{14}C]TDPA could be due to degradation by the acid of the small quantities of [^{14}C]TDPA present.

Tissue radioactivity levels indicate that large oral doses of [^{14}C]TDPA lead neither to preferential incorporation of the label into tissues nor to a significant increase in the general tissue radioactivity.

Rats fed [^{14}C]TDPS showed a slight initial increase in the level of radioactivity in most tissues and slightly larger incorporation into the fat.

These levels declined to background values by day 34. This radioactivity could arise from TDPS partially absorbed as fat-soluble esters which may be widely disseminated but are fairly rapidly eliminated.

Feeding of large doses of DDTDP led to some retention of radioactivity by fat. This radioactivity stil remained after 34 days.

The intake levels encountered in use at the maximum allowable daily intake would be markedly lower than the doses used in this study and it is expected that there would be rapid elimination of all these substances, probably as thiodipropionic acid and the constituent moieties, with negligible retention by the organism.

Table 1: Elimination of rats fed [^{14}C]TDPA, [^{14}C]DDTDP and [^{14}C]TDPS

Compound	Rat	Dose				Time	Elimination (% of dose)			
	No.	Method [a]	mg	mg/kg	µCi	(days)	Urine	CO_2	Feces	Totals
[^{14}C]TDPA	1	Gavage	1.0	3.1	9.3	4	90.1	3.1	0.5	93.6
	2	Gavage	152	650	9.0	4	78.1	8.2	0.5	86.8
	3	Gavage	160	572	9.3	4	84.5	2.8	0.9	88.4
	4	Gavage	152	551	8.9	8	88.5	7.2	0.2	95.9
	5	Feed	55	241	8.2	34	87.4	3.3 [a]	0.1 [b]	90.7
[^{14}C]DDTDP	1	Gavage	32	107	3.3	4	84.6	2.9	3.5	90.9
	2	Gavage	64	208	6.6	8	88.5	3.9	1.8	94.2
	3	Feed	36	166	4.0	34	86.1	3.2 [a]	0.1 [b]	89.4
[^{14}C]TDPS	1	Feed	1.4	5.6	6.9	4	94.7	5.9	0.7	101.2
	2	Feed	1.3	4.8	6.2	8	95.4	5.3	0.6	101.3
	3	Feed	1.1	4.7	5.3	34	97.6	7.4 [a]	0.7 [b]	105.6

[a] By direct scintillation assay; others by $BaCO_3$ procedure
[b] By hydrolysis and direct assay; others by extraction and combustion.

Table 2: Recovery of [^{14}C]TDPA from rat urine by isotope dilution [a]

Material fed	Dose (mg/kg)	Treatment [b]	% of urine radioactivity [c]
[^{14}C]TDPA	3.1	pH to 10 and then to <2	7.0 (2)
		Acid hydrolysis (3N) with added TDPA	104.6 (2)
	627	pH to 10 and then to <2	80.9 (2)
		Acid hydrolysis (3N) with added TDPA	107.3 (2)
[^{14}C]DDTDP	107	Acid hydrolysis (3N) with added TDPA	93.3 (3)
	208	Acid hydrolysis (3N) with added TDPA	100.0 (3)
	166	Acid hydrolysis (3N) with added TDPA	100.0 (3)
[^{14}C]TDPS	5.6	None	3.5 (5)
		Acid hydrolysis (6N), no added TDPA	66.7 (3)

[a] TDPA and TDPS by Geiger counter, DDTPD by scintillation spectrometer. Each value is a single experiment
[b] None indicates addition of TDPA and recrystallization at pH 2
[c] Number in parentheses indicated number of recrystallizations

Conclusion : The results show that esters of TDPA are almost completely absorbed and hydrolyzed to TDPA, which is itself largely eliminated in the urine, either as the free acid or conjugated.

Reliability : (1) valid without restriction
10.04.2003 (7)

5.1.1 ACUTE ORAL TOXICITY

Type : LD50
Value : > 2500 mg/kg bw

Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	other: olive oil
Doses	:	2000, 2500 mg/kg bw
Method	:	
Year	:	1947
GLP	:	no
Test substance	:	Chemical name: 3,3'-thiodipropionic acid, didodecyl ester (CAS No. 123-28-4) Purity: >97% w/w
Method	:	Groups of 5 or 10 rats were dosed orally with 2000 or 2500 mg/kg, respectively. Test material was dissolved in olive oil. Dosed animals were observed for 7 days after dosing.
Result	:	There were no deaths observed at either dose level.
Reliability	:	(2) valid with restrictions

10.04.2003 (8)

Type	:	LD50
Value	:	> 5000
Species	:	rat
Strain	:	no data
Sex	:	male
Number of animals	:	
Vehicle	:	physiol. saline
Doses	:	50, 500, 5000 mg/kg bw
Method	:	
Year	:	1973
GLP	:	no
Test substance	:	Chemical name: 3,3'-thiodipropionic acid, didodecyl ester (CAS No. 123-28-4) Purity: >97% w/w
Method	:	A group of 12 male rats was dosed with 5000 mg/kg while groups of 10 male rats were dosed with 50 or 500 mg/kg. Animals were necropsied on day 6.
Result	:	All animals survived to the scheduled necropsy and appeared normal during the 5 day observation period. No gross morphological changes were observed.
Reliability	:	(2) valid with restrictions

07.04.2003 (6)

Type	:	LD50
Value	:	> 2000 mg/kg bw
Species	:	mouse
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	other: olive oil
Doses	:	300, 500, 1000, 2000 mg/kg
Method	:	
Year	:	1947
GLP	:	no
Test substance	:	Chemical name: 3,3'-thiodipropionic acid, didodecyl ester (CAS No. 123-28-4) Purity: >97% w/w
Method	:	Groups of 19, 10, 20 or 20 mice were dosed orally with 300, 500, 1000 or 2000 mg/kg, respectively. Test material was dissolved in olive oil. Animals were observed for one week after dosing with the test material.

Result	:	There were 4, 0, 0, 1 deaths observed at 300, 5000, 1000 and 2000 mg/kg, respectively. No further information was provided.
Reliability	:	(2) valid with restrictions
07.04.2003		(8)
Type	:	LD50
Value	:	2000 mg/kg bw
Species	:	mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	
Year	:	1951
GLP	:	
Test substance	:	Thiodipropionic acid (CAS No. 111-17-1) Purity: No data
Method	:	No Experimental details available
Reliability	:	(4) not assignable
11.04.2003		(5)
Type	:	LD50
Value	:	3000 mg/kg bw
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	
Year	:	1951
GLP	:	
Test substance	:	Thiodipropionic acid (CAS No. 111-17-1) Purity: No data
Method	:	No Experimental details available
Reliability	:	(4) not assignable
11.04.2003		(5)

5.4 REPEATED DOSE TOXICITY

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	13 weeks
Frequency of treatm.	:	daily
Post exposure period	:	4 weeks
Doses	:	125, 350, 1000 mg/kg/day
Control group	:	yes
NOAEL	:	350 mg/kg bw
NOEL	:	125 mg/kg bw
Method	:	
Year	:	1993
GLP	:	yes

Test substance : Chemical name: 3,3'-thiodipropionic acid, didodecyl ester (CAS No. 123-28-4)
Purity: >97% w/w

Method : Test subjects:

Age at study initiation: 6 weeks, males 162-193g, females 142-180g.

No. of animals/sex/dose: 10 rats/sex/group

Study Design:

Vehicle: 1% carboxymethyl cellulose in water.

Clinical observations:
All animals were observed twice daily for morbidity and mortality. Clinical observations were done daily, with full clinical evaluations done weekly. Body weights and food consumption were recorded weekly. Ophthalmoscopy was performed on all animals pretest and at week 13 in the control and high dose animals. Clinical pathology was performed on 10 animals/sex in control and high dose groups after week 4, 10 animals/sex in all groups after week 13, and in all recovery animals after week 17. Parameters included hematology (except on treatment-free period animals), blood clinical chemistry and urinalysis.

Organs examined at necropsy: All animals were submitted to full necropsy. Organ weights were taken at necropsy. Histopathology was performed on all selected organs/tissues for all animals in the control and high dose groups, the liver, kidneys and lungs for all animals in all groups, and the heart from animals in groups 2 and 3 and in all recovery group animals. The hearts from all animals was examined after PTAH staining. Organs examined histologically also included the epidymides, mammary glands, ovaries, prostate, seminal vesicles, testes, uterus (horn + cervix).

Result : Body weight: No treatment related differences in body weight gain.

Food/water consumption: Unaffected by treatment.

Mortality: No unscheduled deaths.

Clinical signs: No treatment related clinical signs

Ophthalmology: No treatment related eye lesions.

Hematology: None of the hematologic parameters were considered to represent an adverse effect of treatment.

Urine: Urine parameters were unaffected other than being slightly more acidic in the high dose animals as compared to the controls. This was reversible after the 4 week treatment-free period.

Clinical chemistry: None of the clinical chemistry parameters other than a reversible elevation in serum cholesterol in the high dose females and a reversible elevation of alanine and aspartate aminotransferase activities in all high dose animals were related to an effect of treatment.

Gross pathology: Macroscopic changes were considered to either be agonal or incidental in origin or unrelated to treatment. Treatment related microscopic lesions were seen in the heart of high dose animals. The lesion was described as small foci of degenerated or necrotic fibers associated with minimal to moderate mononuclear cell infiltration. This association suggested early or ongoing myocarditis. These lesions were

not present in animals previously treated at the high dose level but allowed a 4 week period without treatment. There were no other treatment related microscopic lesions.

Organ weight changes: Minor differences in the weight of the major organs were considered of no toxicological significance in the absence of microscopic lesions.

Conclusion : The oral (gavage) administration of the test material to the rat for 13 weeks at a dose level of 1000 mg/kg/day was associated with a minor increase in serum cholesterol concentrations in females, increased serum ALAT and ASAT activities and decreased urinary pH in both sexes.

Microscopic findings in the heart of these animals suggested as ongoing myocarditis. The heart was therefore identified as the target organ. All these changes were reversible after 4 weeks without treatment. At a dose level of 350 mg/kg/day there was no evidence for any treatment related microscopic effect in the heart. Females at this dose exhibited a very small, but not significantly significant, increase in Hb concentrations. These individual values fell in the normal background range and are considered unlikely to be a direct toxic effect of the test material. Clinical chemistry results indicated calcium concentrations of the males were slightly elevated compared with controls. However, the differences were small, not statistically significant and generally well within the normal background range. No other differences to indicate an adverse effect of the test material were noted. This dose level is therefore considered to be the no observed adverse effect level for the test material in the rat. There were no changes considered to represent an effect of the test material at 125 mg/kg/day and therefore this dose level is considered to be the no observed effect level for the test material in the rat.

Reliability : (2) valid with restrictions
07.05.2003 (1)

5.5 GENETIC TOXICITY 'IN VITRO'

5.6 GENETIC TOXICITY 'IN VIVO'

5.8.1 TOXICITY TO FERTILITY

Type	:	other
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	13 weeks + 4 weeks post exposure
Frequency of treatm.	:	daily
Premating exposure period		
Male	:	
Female	:	
Duration of test	:	
No. of generation studies	:	
Doses	:	125, 350, 1000 mg/kg/day
Control group	:	
Method	:	
Year	:	1993
GLP	:	yes

Test substance : Chemical name: 3,3'-thiodipropionic acid, didodecyl ester (CAS No. 123-28-4)
Purity: >97% w/w

Method : Test subjects:

Age at study initiation: 6 weeks, males 162-193g, females 142-180g.

No. of animals/sex/dose: 10 rats/sex/group

Study Design:

Vehicle: 1% carboxymethyl cellulose in water.

Clinical observations:
All animals were observed twice daily for morbidity and mortality. Clinical observations were done daily, with full clinical evaluations done weekly. Body weights and food consumption were recorded weekly. Ophthalmoscopy was performed on all animals pretest and at week 13 in the control and high dose animals. Clinical pathology was performed on 10 animals/sex in control and high dose groups after week 4, 10 animals/sex in all groups after week 13, and in all recovery animals after week 17. Parameters included hematology (except on treatment-free period animals), blood clinical chemistry and urinalysis.

Organs examined at necropsy: All animals were submitted to full necropsy. Organ weights were taken at necropsy. Histopathology was performed on all selected organs/tissues for all animals in the control and high dose groups, the liver, kidneys and lungs for all animals in all groups, and the heart from animals in groups 2 and 3 and in all recovery group animals. The hearts from all animals were examined after PTAH staining. Organs examined histologically also included the epidymides, mammary glands, ovaries, prostate, seminal vesicles, testes, uterus (horn + cervix).

Result : NOAEL = 350 mg/kg/day

NOEL = 125 mg/kg/day

Body weight: No treatment related differences in body weight gain.

Food/water consumption: Unaffected by treatment.

Mortality: No unscheduled deaths.

Clinical signs: No treatment related clinical signs

Ophthalmology: No treatment related eye lesions.

Hematology: None of the hematologic parameters were considered to represent an adverse effect of treatment.

Urine: Urine parameters were unaffected other than being slightly more acidic in the high dose animals as compared to the controls. This was reversible after the 4 week treatment-free period.

Clinical chemistry: None of the clinical chemistry parameters other than a reversible elevation in serum cholesterol in the high dose females and a reversible elevation of alanine and aspartate aminotransferase activities in all high dose animals were related to an effect of treatment.

Gross pathology: Macroscopic changes were considered to either be agonal or incidental in origin or unrelated to treatment. Treatment related microscopic lesions were seen in the heart of high dose animals. The

lesion was described as small foci of degenerated or necrotic fibers associated with minimal to moderate mononuclear cell infiltration. This association suggested early or ongoing myocarditis. These lesions were not present in animals previously treated at the high dose level but allowed a 4 week period without treatment. There were no other treatment related microscopic lesions.

Organ weight changes: Minor differences in the weight of the major organs were considered of no toxicological significance in the absence of microscopic lesion.

Conclusion : This study included specific evaluation of the reproductive organs of the test animals. No adverse effects on these organs were seen at the dose levels used in this study. This is suggestive of no adverse effects on reproduction.

Reliability : (2) valid with restrictions
07.05.2003 (1)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	Wistar
Route of admin.	:	gavage
Exposure period	:	days 6-15 of gestation
Frequency of treatm.	:	
Duration of test	:	
Doses	:	16, 74, 350 or 1600 mg/kg in corn oil
Control group	:	yes
NOAEL maternal tox.	:	1600 mg/kg bw
NOAEL teratogen.	:	1600 mg/kg bw
Method	:	other: essentially follows OECD 414
Year	:	1972
GLP	:	no
Test substance	:	Chemical name: 3,3'-thiodipropionic acid, didodecyl ester (CAS No. 123-28-4) Purity: not stated

Method : A positive control group received 250 mg/kg aspirin. Frequency of treatment for positive control group not stated. The number of pregnant rats at the end of the study ranged from 19-21/dose level. Feed and water were available ad libitum. The rats were observed daily for general appearance and behaviour, with emphasis on feed consumption and weight. Weights were obtained on days 0, 6, 11, 15 and 20 of gestation. On day 20 of gestation caesarian sections were performed and the numbers of implantation and resorption sites as well as the numbers of live and dead fetuses were recorded. The urogenital tract of each dam was examined for any abnormality, all fetuses were examined for any gross external abnormalities, and all live pups were weighed. Visceral examinations were performed on one-third of the fetuses of each litter, and the remaining two-thirds were examined for skeletal defects.

Result : No adverse effects with respect to number of implantations and maternal or fetal death were noted after oral administration to rats of up to 1600 mg/kg dilauryl thiodipropioinc acid on days 6-15 of gestation. There were no significant differences in numbers of abnormalities of the soft or skeletal tissues between the treated and sham control fetuses.

Reliability : (2) valid with restrictions
07.05.2003 (4)

Species	:	mouse
Sex	:	female

Strain	:	CD-1
Route of admin.	:	gavage
Exposure period	:	days 6-15 of gestation
Frequency of treatm.	:	daily
Duration of test	:	
Doses	:	16, 74, 350 and 1600 mg/kg in corn oil
Control group	:	yes
NOAEL maternal tox.	:	1600 mg/kg bw
NOAEL teratogen.	:	1600 mg/kg bw
Method	:	other: essentially follows OECD 414
Year	:	1972
GLP	:	no
Test substance	:	Chemical name: 3,3'-thiodipropionic acid, didodecyl ester (CAS No. 123-28-4) Purity: not stated
Method	:	A positive control group received 150 mg/kg aspirin. Frequency of treatment for the positive control not stated. The number of pregnant mice at the end of the study ranged from 20-22/dose level. Feed and water were available ad libitum. The mice were observed daily for general appearance and behaviour, with emphasis on feed consumption and weight. Weights were obtained on days 0, 6, 11, 15 and 17 of gestation. On day 17 of gestation, caesarian sections were performed and the numbers of implantation and resorption sites, as well as the numbers of live and dead fetuses, were recorded. The urogenital tract of each dam was examined for any abnormality, all fetuses were examined for any gross external abnormalities, and all live pups were weighed. Visceral examinations were performed on one-third of the fetuses of each litter, and the remaining two-thirds were examined for skeletal defects.
Result	:	No adverse effects were found with respect to implantations and maternal and fetal survival after oral administration to mice of up to 1600 mg/kg test material on days 6-15 of gestation. The number of abnormalities seen in the soft or skeletal tissues of the treated fetuses was comparable to that seen in the sham control fetuses.
Reliability 07.05.2003	:	(2) valid with restrictions (4)

Species	:	rabbit
Sex	:	female
Strain	:	Dutch
Route of admin.	:	gavage
Exposure period	:	days 6-18 of gestation
Frequency of treatm.	:	daily
Duration of test	:	
Doses	:	2.5, 10, 45, 216, 1000 mg/kg in corn oil
Control group	:	yes
NOAEL maternal tox.	:	1000 mg/kg bw
NOAEL teratogen.	:	1000 mg/kg bw
Method	:	other: essentially follows OECD 414
Year	:	1973
GLP	:	no
Test substance	:	Chemical name: 3,3'-thiodipropionic acid, didodecyl ester (CAS No. 123-28-4) Purity: not stated
Method	:	Groups of 15-29 artificially inseminated females/dose level resulted in 8-13 pregnant rabbits/dose level. On day 29, all does were subjected to caesarian section. The numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of the live pups were also recorded. The urogenital tract of each animal was examined in detail for normality. All fetuses underwent a detailed gross examination for the presence of external congenital

abnormalities. The live fetuses of each litter were then placed in an incubator for 24 hours for the evaluation of neonatal survival. All surviving pups were sacrificed, and all pups examined for visceral abnormalities by dissection. All fetuses were then cleared in potassium hydroxide, stained with alizarin red S dye and examined for skeletal defects.

Result : Eight to thirteen pregnant dams survived to term. There was no clearly discernible effect on nidation or on maternal or fetal survival at doses as high as 1000 mg/kg. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the control.

Reliability : (2) valid with restrictions
07.05.2003 (3)

Species	:	hamster
Sex	:	female
Strain	:	other: Golden
Route of admin.	:	gavage
Exposure period	:	days 6-10 of gestation
Frequency of treatm.	:	daily
Duration of test	:	
Doses	:	16, 74, 350 or1600 mg/kg in corn oil
Control group	:	yes
NOAEL maternal tox.	:	1600 mg/kg bw
NOAEL teratogen.	:	1600 mg/kg bw
Method	:	other: essentially follows OECD 414
Year	:	1972
GLP	:	no
Test substance	:	Chemical name: 3,3'-thiodipropionic acid, didodecyl ester (CAS No. 123-28-4) Purity: not stated

Method : The number of hamsters at the end of the study ranged from 20-23/dose level. Feed and water were available ad libitum. The hamsters were observed daily for general appearance and behaviour, with emphasis on feed consumption and weight. Weights were obtained on days 0, 8, 10 and 14 of gestation. On day 14 of gestation caesarian sections were performed and the numbers of implantation and resorption sites as well as the numbers of live and dead fetuses were recorded. The urogenital tract of each dam was examined for any abnormality, all fetuses were examined for any gross external abnormalities, and all live pups were weighed. Visceral examinations were performed on one-third of the fetuses of each litter, and the remaining two-thirds were examined for skeletal defects.

Result : The numbers of implantations and maternal and fetal survival were not adversely affected by oral administration to hamsters of up to 1600 mg/kg test material on days 6-10 of gestation. No significant differences in the number of soft or skeletal tissue abnormalities were found between treated and sham control fetuses.

Reliability : (2) valid with restrictions
07.05.2003 (4)

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(2) Crompton Corporation, Mark 5152 Safety Data Sheet v1, April 24, 2002; Chevron Phillips Chemical Co., Dimethyl Thiodipropionate Material Safety Data Sheet, MSDS #644740, rev. #1, February 21, 2002

(3) FDA (1973). Teratologic evaluation of FDA 71-40 (dilauryl thiodipropioinc acid) NTIS PB-223 824: Reported in, Thioesters Association, Thiodipropionates Category Robust Summaries, EPA HPV Chemical Challenge Program, December 2001

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(5) Lehman, A.J., et al, Advanc. Food Res., 3, 197, 1951; Reported in Eighth Report of th eJoint FAO/WHO Expert Committee on Additives, Wld Hlth Org. techn. Rep. Ser., 1965, 309; FAO Nutrition Meetings Report seriess 1965, 38

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(8) Tullar, P.E. (1947) The pharmacology and toxicology of thiodipropionic acid and its dilauryl and distearyl esters. Final Report. The Kalusowski Memorial Research Laboratories, School of Pharmacy, The George Washington University, Washington D.C. Unpublished data: Reported in, Thioesters Association, Thiodipropionates Category Robust Summaries, EPA HPV Chemical Challenge Program, December 2001

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